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Catalytic amino acid production from biomass-derived intermediates

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Amino acids are the building blocks for protein biosynthesis and find use in myriad industrial applications including in food for humans, in animal feed, and as precursors for bio-based plastics, among others. However, the development of efficient chemical methods to convert abundant and renewable feedstocks into amino acids has been largely unsuccessful to date. To that end, here we report a heterogeneous catalyst that directly transforms lignocellulosic biomass-derived α -hydroxyl acids into α -amino acids, including alanine, leucine, valine, aspartic acid, and phenylalanine in high yields. The reaction follows a dehydrogenation-reductive amination pathway, with dehydrogenation as the rate-determining step. Ruthenium nanoparticles supported on carbon nanotubes (Ru/CNT) exhibit exceptional efficiency compared with catalysts based on other metals, due to the unique, reversible enhancement effect of NH_3 on Ru in dehydrogenation. Based on the catalytic system, a two-step chemical process was designed to convert glucose into alanine in 43% yield, comparable with the well-established microbial cultivation process, and therefore, the present strategy enables a route for the production of amino acids from renewable feedstocks. Moreover, a conceptual process design employing membrane distillation to facilitate product purification is proposed and validated. Overall, this study offers a rapid and potentially more efficient chemical method to produce amino acids from woody biomass components.

amino acids | α -hydroxyl acids | amination | catalysis | ruthenium

As the basic building blocks of proteins, amino acids play an essential role in life and are widely used in food and feed supplements, as precursors to biodegradable plastics, pharmaceutical products, and elsewhere (1). Although the current production of amino acids mainly relies on microbial cultivation processes, the issues associated with the scale limitations of microbial processes, the strict need for sterile operating conditions, and the complexity of their separation have stimulated efforts to develop efficient chemical approaches to produce amino acids and their derivatives (2–5).

The Strecker reaction is a classical chemical approach to produce amino acids (6), which employs highly toxic cyanides as nitrogen sources and nonrenewable aldehydes. The selective oxidation of amino alcohols and/or aldehydes serves as another option (7). In this procedure, protection/deprotection strategies for amino groups and/or stoichiometric, hazardous oxidants are often involved. Furthermore, the nitrogen is provided by the substrates, which are not always easily accessible. To date, sustainable and generalizable approaches for the direct synthesis of amino acids from abundant and renewable feedstocks using NH_3 are still quite rare.

The catalytic transformations of various biomass components, including polysaccharides, lignin, and their derivatives, into valuable oxygen-containing chemicals (8–15) have been intensively studied (16–21). One prominent example, among others, is the conversion of biomass to α -hydroxypropanoic acid (i.e., lactic acid) (22–26). Lanthanide-based catalysts afford ca. 90% lactic acid directly from

cellulose under hydrothermal conditions (24), whereas barium hydroxide catalyzes the quantitative conversion of glucose into lactic acid at room temperature (26). Several other α -hydroxyl acids are also readily available from lignocellulosic biomass. Cellulose may be converted into glycolic acid via selective oxidation over heteropoly acids (27) and into phenyllactic acid biocatalytically (28). Erythrose, a tetrose, can be transformed to vinylglycolate in the presence of tin salts (29) and further to α -hydroxyl butyric acid via hydrogenation. Simple base treatment enables the isolation of *p*-coumaric acid from grass lignins (30), which can be converted to *p*-hydroxyphenyllactic acid by hydration.

Because biomass-derived α -hydroxyl acids are readily accessible, we envisaged that the direct amination of these acids with ammonia could offer a promising and general method for amino acid synthesis (Fig. 1). Although homogeneous catalysis has proven success in producing primary amines from alcohols (31–33), recyclable heterogeneous catalysts are very limited, and the catalyst function is not well understood (34–37). Herein, we report an efficient heterogeneous catalytic system for the amination of multiple α -hydroxyl acids into corresponding amino acids using

Significance

Today, amino acids are primarily manufactured via microbial cultivation processes, which are costly, are time consuming, and require extensive separations processes. As an alternative, chemocatalytic approaches to produce amino acids from renewable feedstocks such as bio-based sugars could offer a rapid and potentially more efficient means of amino acid synthesis, but efforts to date have been limited by the development of facile chemistry and associated catalyst materials to selectively produce α -amino acids. In this work, various α -amino acids, including alanine, leucine, aspartic acid, and phenylalanine, were obtained from both biomass-derived α -hydroxyl acids and glucose. The route bridges plant-based biomass and proteinogenic α -amino acids, offering a chemical approach that is potentially superior to microbial cultivation processes.

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The authors declare no conflict of interest.

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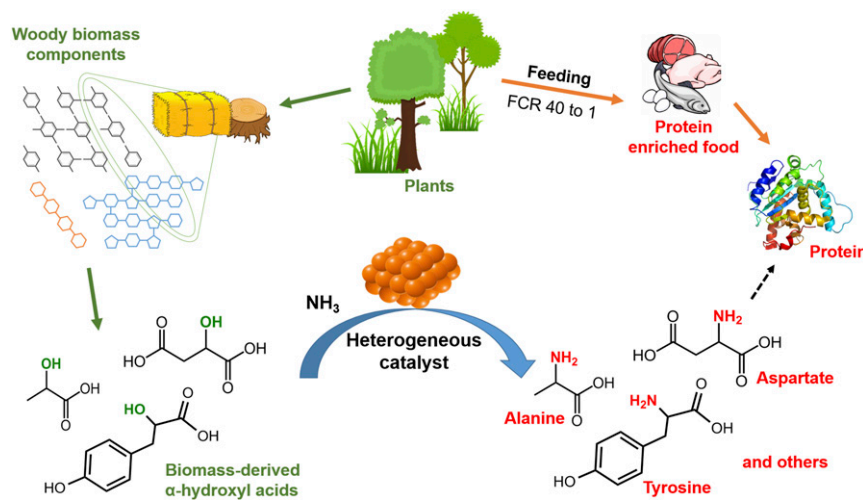


Fig. 1. Catalytic transformation of biomass-derived α -hydroxyl acids into amino acids.

ammonia, including alanine, leucine, aspartic acid, and others in good to excellent yields. Based on the catalytic system, a chemical process transforming glucose to alanine via lactic acid as an intermediate was established, providing alanine yield higher than some of the best values obtained in microbial cultivation processes found in literature (38).

Results and Discussion

We first aimed to develop a robust amination catalyst and associated process on a model α -hydroxyl acid. Accordingly, amination of lactic acid was initially conducted over several noble metal nanoparticles (NPs) loaded on carbon nanotubes (CNT) and Raney Ni in a batch reactor. The catalysts were prepared by impregnation of metal precursors on CNT, followed by treatment in a H_2/N_2 (5%) atmosphere at 673 K to ensure complete reduction of the metals. X-ray diffraction (XRD) and transmission electron microscopy (TEM) confirm that the metal NPs are well dispersed on the support and possess similar sizes (*SI Appendix, Figs. S1 and S2*). Evaluation of the catalysts in lactic acid conversion in aqueous ammonia at 493 K for 2 h (Fig. 2A) shows that the Ru/CNT is the most effective, providing alanine in 49% yield. Rh/CNT, Pt/CNT, and Raney Ni afford alanine in yields of 14, 12, and 8%, respectively, whereas Pd/CNT and Ir/CNT were inactive. Ru NPs loaded on five other supports were further prepared and evaluated (Fig. 2B). The alanine yields were distributed in a narrow range between 32 and 38%, irrespective of the nature of support, i.e., whether it is acidic/basic, reducible/nonreducible, with the catalyst based on the CNT support remaining the most effective.

Fig. 3A shows two possible routes for alanine formation comprising indirect (pathway I) and direct (pathway II) pathways. The indirect path (I) includes the dehydrogenation to a ketone, the reaction of the ketone with ammonia to afford an imine, followed by hydrogenation (39), whereas the direct path (II) involves a S_N2 substitution of the -OH group with an $-NH_2$ group. If the absence of an α -H in the substrate does not affect the formation of the amino acid, the reaction should proceed via direct amination; otherwise, the indirect route will be dominant. We conducted the amination of α -hydroxyl isobutyric acid—a tertiary alcohol without an α -H—under various conditions (*SI Appendix, Table S1*). Amino acid formation was not observed in any test, suggesting that the α -H is crucial, which rules out the possibility of direct amination, i.e., pathway II. The indirect pathway (I) involves dehydrogenation and hydrogenation steps, and therefore, the concentration of hydrogen gas should influence the reaction. Indeed, a direct relationship

between the hydrogen pressure and the alanine yield was observed in the pressure range tested (0–1 MPa) (*SI Appendix, Table S2*). Pathway I is reminiscent of the biosynthesis of various amino acids from glucose where pyruvate is often a key intermediate (1).

Following the indirect amination pathway (I), noble metals, in particular Pd and Pt, should show high efficiency because of their well-known ability in dehydrogenation/hydrogenation (40). However, our experiments show that only Ru-based catalysts are effective (Fig. 2A). We hypothesize that there are three possible origins for the unique performance of Ru: (i) the in situ formed α -keto acid could only be effectively converted to the amino acid by the Ru catalyst (steps 2 and 3 in pathway I); (ii) alanine decomposes over other metal catalysts under the reaction conditions; or (iii) the ability of other metal catalysts to perform the dehydrogenation step is suppressed in the presence of other reagents (e.g., NH_3), whereas it is maintained or even enhanced by the Ru/CNT catalyst (step 1 in pathway I).

We first tested the reductive amination of pyruvic acid (41), a key dehydrogenation intermediate of lactic acid (*SI Appendix, Table S3*). All five noble metal catalysts (i.e., Ru, Pd, Pt, Rh, and Ir) exhibit similar activity and selectivity, showing that the transformation of dehydrogenated intermediates into amino acids can be achieved by all of the catalysts. We next compared the stability of alanine in the presence of the Pd/CNT and Ru/CNT (*SI Appendix, Table S3*). In a blank experiment, i.e., at 493 K for 2 h

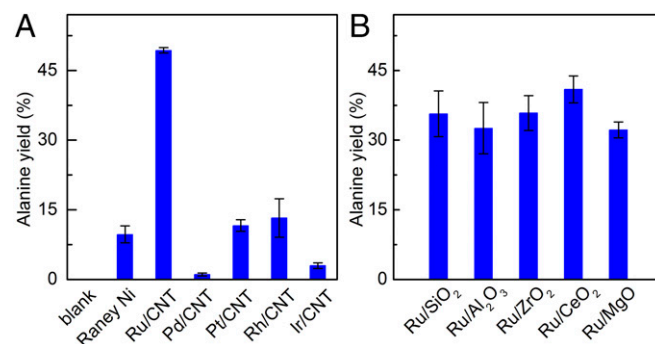


Fig. 2. Catalytic conversion of lactic acid to alanine in a batch reactor. (A) Alanine yield with different metal catalysts. (B) Alanine yield across Ru-based catalysts on different supports. Reaction conditions: 0.5 mmol lactic acid, metal/substrate molar ratio = 0.025, 2.5 mL $NH_3 \cdot H_2O$ (25 wt %), 1 MPa H_2 , 493 K, 2 h. Error bars indicate SDs.

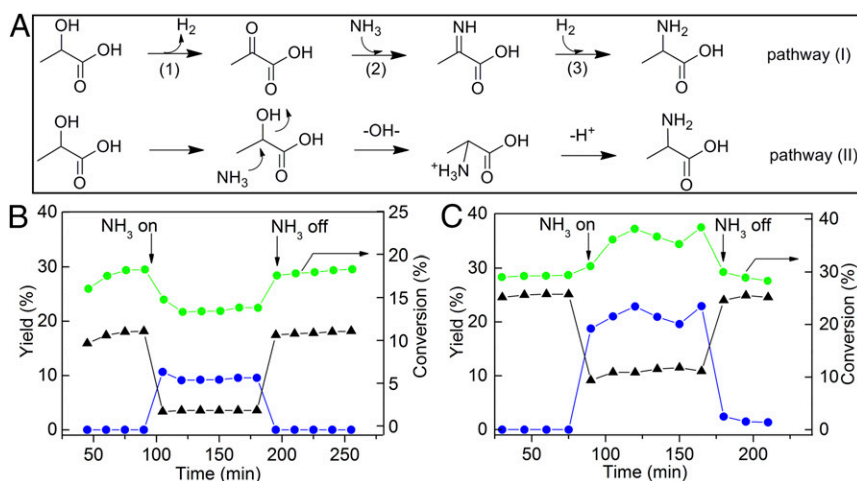


Fig. 3. (A) Two possible reaction pathways for amination of lactic acid to alanine. (B) Dehydrogenation of isopropanol catalyzed by Pd/CNT and (C) Ru/CNT under a H₂ atmosphere in a fixed-bed flow reactor. Green circles indicate isopropanol conversion, black triangles indicate acetone yield, and blue circles indicate isopropylamine yield. Reaction conditions: 50 mg catalyst, 2 μ L/min isopropanol, 50 mL/min total flow rate, 473 K, 8 mL/min NH₃ flow rate.

without catalyst, 17% of the alanine decomposed. The number only slightly increased to 20% with Pd/CNT, suggesting that the catalysts do not induce significant product decomposition. These experiments ruled out the hypotheses *i* and *ii*.

Consequently, isopropanol dehydrogenation on different catalysts was compared in a fixed-bed flow reactor. H₂ was supplied in the reaction, mimicking the conditions used in the lactic acid amination, with NH₃ gas switching on and off to evaluate its influence on dehydrogenation. In the absence of NH₃, both catalysts were active: Ru/CNT yielded ca. 25% acetone, whereas Pd/CNT yielded ca. 20%. Surprisingly, turning on NH₃ led to a significant decrease (\sim 25%) of isopropanol conversion with Pd/CNT (Fig. 3B) but a remarkable increase (\sim 30%) with Ru/CNT (Fig. 3C). Isopropyl amine and acetone were the two major products. The combined yields of the two with Ru/CNT were two times higher than with Pd/CNT, although the two catalysts exhibited comparable activities in the absence of NH₃. Stopping the NH₃ supply led to the recovery of both catalysts to their original activity and selectivity. These observations demonstrate a strong and reversible influence of NH₃ on the dehydrogenation ability of Ru and Pd NPs; the former was enhanced, and the latter was suppressed. This effect has been further verified over commercial Ru and Pt catalysts (SI Appendix, Fig. S5), substantiating the unique activity enhancement of Ru catalysts by NH₃. Note that the NH₃ concentration in the batch reactor is

much higher than in the flow reactor, and thus, the promotional effect of NH₃ on Ru and the inhibition effects on other metals may be even more pronounced.

The activity of some Ru complexes for hydrogenation is remarkably enhanced with the addition of one equivalent of diamine because the ligand and the Ru metal work cooperatively to activate substrates (42). To test whether this promotional effect exists on the surface of Ru NPs, the hydrogenation of acetophenone was conducted with and without an ethylenediamine/KOH couple (SI Appendix, Table S4). In the presence of the two, acetophenone conversion was enhanced from 27 to 69% over the Ru/CNT catalyst. In contrast, no promotional effect on Pt/CNT and an inhibition effect on Pd/CNT were observed. As such, NH₃ plausibly coordinates to the Ru surface to activate Ru by modifying its d-band center. NH₃ also works synergistically with Ru to activate alcohol substrates by deprotonation of the OH group, in a similar manner to Ru homogeneous complexes (42).

The kinetic profile of the reaction with the Ru/CNT catalyst shows that the initial selectivity of alanine was ca. 70% (at 0.5 h) and only slightly decreases afterward (SI Appendix, Fig. S6). No pyruvic acid intermediate was detected, in agreement with the observation that the amination of the keto acid readily occurs. The dehydrogenation step is rate-determining and is favored at high temperatures; hence, a minimum temperature of 433 K is required (SI Appendix, Fig. S7).

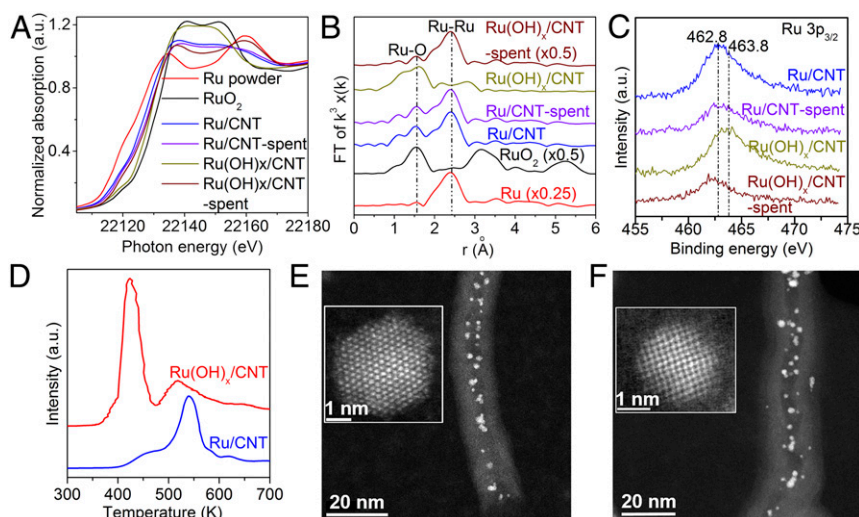


Fig. 4. (A) Ru K-edge XANES spectra of various catalysts. (B) Fourier transformed Ru K-edge EXAFS spectra for fresh and spent Ru/CNT and Ru(OH)_x/CNT catalysts. (C) XPS spectra of Ru 3p for fresh and spent Ru/CNT, Ru(OH)_x/CNT catalysts. (D) H₂-TPR profile of Ru/CNT and Ru(OH)_x/CNT. STEM images of (E) fresh Ru/CNT and (F) spent Ru/CNT.

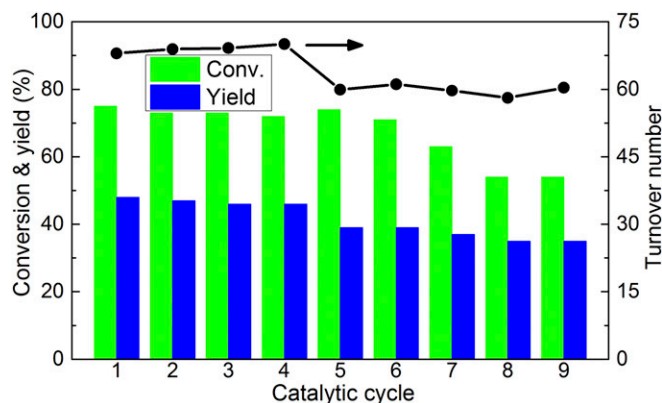


Fig. 5. Ru/CNT recycling test for catalytic conversion of lactic acid to alanine. Reaction conditions: 0.5 mmol lactic acid, 50 mg Ru/CNT (Ru loading 3 wt %), 2.5 mL $\text{NH}_3\text{H}_2\text{O}$ (25 wt %), 1 MPa H_2 , 493 K, 2 h. Turnover number of each catalytic cycle is calculated based on Ru dispersion of fresh Ru/CNT catalyst and the total Ru in the system.

An $\text{Ru}(\text{OH})_x/\text{CNT}$ catalyst with Ru in high-oxidation states was prepared for comparison. The $\text{Ru}(\text{OH})_x/\text{CNT}$ catalyst resulted in slightly lower activity and selectivity to alanine than Ru/CNT catalyst (*SI Appendix, Fig. S8*). X-ray absorption near edge structure (XANES; Fig. 4A), extended X-ray absorption fine structure (EXAFS; Fig. 4B), X-ray photoelectron spectroscopy (XPS; Fig. 4C), and H_2 -temperature programmed reduction (H_2 -TPR; Fig. 4D) analysis suggested that Ru species on both fresh and spent Ru/CNT catalyst are mainly metallic with a small fraction of positive charges, whereas in situ reduction of Ru^{3+} into metallic Ru occurred on $\text{Ru}(\text{OH})_x/\text{CNT}$ catalyst, providing strong evidence that Ru(0) is the key catalytic active species. Scanning transmission electron microscopy (STEM) micrographs showed uniformly dispersed Ru NPs on CNT (Fig. 4E and F), which remained unchanged after reaction. However, $\text{Ru}(\text{OH})_x/\text{CNT}$ did not survive under reaction conditions, and amorphously dispersed Ru species became Ru NPs (*SI Appendix, Fig. S4*). The in situ formed Ru NPs on $\text{Ru}(\text{OH})_x/\text{CNT}$ exhibited a larger nanoparticle size than Ru/CNT, which is likely the reason for the lower catalytic activity and lower white line intensity in the XANES spectra.

The stability of Ru/CNT was further tested with recycling experiments (Fig. 5). The performance of the Ru/CNT slightly decreased during repeated cycles: the alanine yield dropped from 48% in the first cycle to 35% in the ninth cycle. The activity loss was partially due to the loss of catalyst during repeated reactions (ca. 1 mg catalyst loss each round). After nine cycles, the accumulated turnover numbers reached 575 per surface Ru atom, considering a Ru dispersion of 24.3% based on H_2 chemisorption experiments (*SI Appendix, Fig. S3 and Table S5*). Hot filtration experiments were conducted to identify the nature of the catalytically active species and the level of leached Ru in solution. The hot filtrate was inactive, suggesting the heterogeneous Ru NPs as the catalytically active species (*SI Appendix, Fig. S6*). Nevertheless, inductively coupled plasma mass spectrometry detected the existence of a small amount of soluble Ru species in the solution, corresponding to 0.37% of the total Ru on Ru/CNT.

To further enhance the dehydrogenation capability of Ru, the Ru/CNT catalyst was modified by introducing a second metal component, and the reaction parameters were evaluated for lactic acid amination (*SI Appendix, Tables S6–S8*). Ni-doped Ru/CNT affords alanine in a yield of 62% under optimized reaction conditions (Table 1). We further attempted to produce alanine directly from glucose via a two-step process. Lactic acid was obtained in 75% yield from glucose at room temperature using $\text{Ba}(\text{OH})_2$ as the catalyst (26). The resulting solution was acidified, freeze-dried, and directly used in the amination step. An overall alanine yield of

43% was obtained (*SI Appendix, Table S9*), which is comparable with the well-established microbial cultivation process (38). Notably, the theoretical alanine yield from glucose in the chemical process is 100%, so that the yield can be further increased through catalyst and process optimization. In contrast, microbial cultivation process cannot reach 100% yield, because a substantial amount of glucose is consumed for cell growth. Moreover, production of certain amino acids, such as tyrosine, via microbial cultivation process is inefficient (43). In contrast, one can conceptually envisage quantitative transformation of *p*-coumarate into tyrosine from grass lignin in several chemical steps. As such, our route represents a competing chemical way for amino acid production with potentially improved yields and much higher space–time productivity.

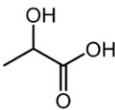
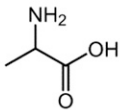
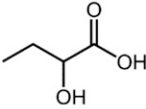
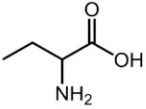
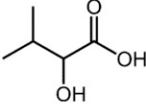
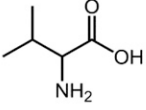
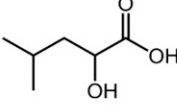
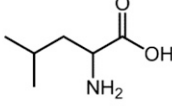
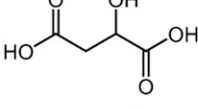
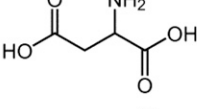
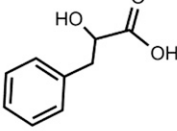
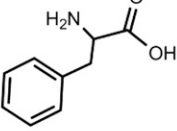
Various amino acids were prepared from biomass-derived α -hydroxyl acids in aqueous ammonia (Table 1 and *SI Appendix, Table S10*). For example, α -aminobutyric acid, valine, and leucine were obtained from α -hydroxyl butyric acid, α -hydroxyl-3-methylbutyric acid, and α -hydroxyisocaproic acid, respectively. By modification of the Ru/CNT catalyst with 10 wt % nickel or simply by adding a small amount of base (e.g., NaOH and KOH) to promote dehydrogenation, the formation of amino acids was markedly enhanced. The yields of α -aminobutyric acid, valine, and leucine reached 73, 60, and 69%, respectively. The synthesis of aspartic acid was also achieved by amination of 2-hydroxysuccinic acid. The yield of 27% is lower than the other substrates tested, possibly due to the steric hindrance of the terminal acid group. In addition to aliphatic acids, the production of phenylalanine was achieved (30% yield) from 3-phenyllactic acid that is potentially derived from lignin. β -hydroxyl acids, such as 3-hydroxypropionic acid, were recently produced from sugar degradation (44), which afforded the starting materials for production of β -amino acids. We tested the transformation of β -hydroxybutyric acid and 3-hydroxypropionic acid in the amination system. Unlike α -hydroxyl acids, both of them afforded low yields toward corresponding amino acids (*SI Appendix, Table S11*), suggesting the current catalytic system is limited to producing α -amino acids.

Prompted by the promising catalytic data, we conceived an integrated process comprising reaction, product purification, and reagent recycling (Fig. 6). Purification of the product is known to be the main cost driver in the amino acid production process (45), which also generates a significant amount of waste salts. Here we propose to utilize membrane distillation (MD) before crystallization to concentrate the amino acids and to recycle the aqueous ammonia solution. An MD-based system was constructed to experimentally demonstrate an initial proof of this concept, where the alanine feed solution was heated to 40 °C–46 °C at one side of the membrane, and the vaporized ammonia and water were collected at the other side by a cold stream of water at 12 °C. Results showed that alanine was maintained in the feed to near 100% retention, and the alanine concentration was increased from 0.020 g/mL to 0.077 g/mL. Compared with a conventional distillation process, the current approach is more energy efficient by consuming around two to three times less energy (*SI Appendix, p. 13*). In addition, the aqueous ammonia in the permeate can be recycled and reused. After membrane distillation, two crystallizers will be used to isolate amino acids and hydroxyl acids in the form of their ammonium salts (46).

Summary

In this work, we developed an efficient heterogeneous catalytic system for the synthesis of various amino acids from biomass-derived α -hydroxyl acids, in which dehydrogenation is rate-determining. Ru exhibits a unique enhancement effect of the dehydrogenation activity in the presence of NH_3 , resulting in superior performance for the reaction. The direct conversion of glucose into alanine is achieved following a simple, two-step chemical protocol. Effective concentration and separation of alanine from ammonia solution was demonstrated by a membrane distillation process. Our work demonstrates the feasibility of chemical transformation

Table 1. Catalytic transformation of different biomass-derived α -hydroxyl acids to corresponding amino acids

Substrate	Product		Yield, %
	Structure	Name	
		Alanine	62*
		α -aminobutyric acid	66 73*
		Valine	48 60*
		Leucine	49 69 [†]
		Aspartic acid	27 [†]
		Phenylalanine [‡]	30*

Reaction conditions: 0.5 mmol substrate, 50 mg Ru/CNT (Ru loading 3 wt %), 2.5 mL $\text{NH}_3\text{H}_2\text{O}$ (25 wt %), 1 MPa H_2 , 493 K, 2 h.

*Ru/CNT was modified with 10 wt % Ni.

[†]KOH or NaOH (1 mmol) was added in the solution.

[‡]Ammonia was removed before derivatization.

of lignocellulosic biomass components into amino acids and opens the way to the production of high-value proteins from agricultural wastes via chemical routes in the future.

Materials and Methods

Catalysts Synthesis. The CNT-supported Ru nanoparticles were prepared by wet impregnation method. Typically, the CNT was added into the aqueous solution of RuCl_3 and then subjected to stirring for 1 h at room temperature. After aging for 2 h, the water was evaporated at 373 K, and the solid product was reduced in H_2/N_2 (5%) gas at 673 K for 1 h. The CNT supported

other metals (e.g., Pd, Pt, and Rh) and Ru loaded on different supports (e.g., Al_2O_3 , SiO_2 , CeO_2 , ZrO_2 , and MgO) were prepared following a similar procedure. $\text{Ru}(\text{OH})\text{x}/\text{CNT}$ was obtained by a precipitation method, in which a diluted solution of NaOH (0.05 M) was slowly added into a mixture of solution of RuCl_3 and CNT, followed by washing and drying. For all of the catalysts, the metal loadings were ~3 wt %.

Catalytic Activity Evaluation. The catalytic transformation of lactic acid and other biomass-derived acids was performed in an autoclave. For example, for the conversion of lactic acid, the Ru/CNT catalyst and lactic acid were added to

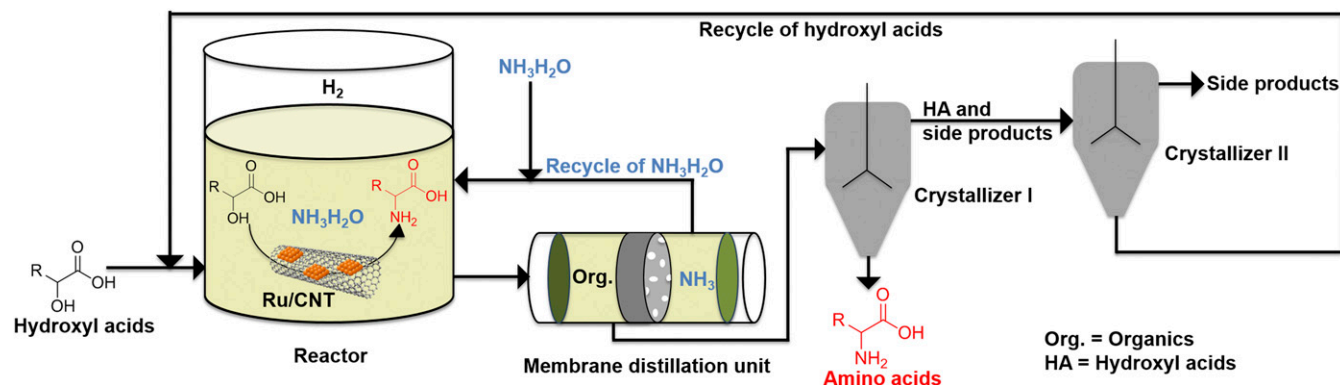


Fig. 6. A conceptual process diagram consists of a reactor, a membrane distillation unit, and two crystallizers.

the reactor that had been precharged with aqueous ammonia. After the introduction of H₂ at a pressure of 1 MPa, the reactor was placed in a metal jacket wafer on an electronic hotplate (typically 493 K). After a fixed time, the reaction was quickly terminated by cooling the reactor to room temperature in cold water. The catalytic transformation of glucose to lactic acid was performed in a round-bottom flask with Schlenk line. Degassed water was added to the reactor that had been precharged with glucose and Ba(OH)₂ under N₂ atmosphere. The flask was put in an oil bath on an electronic stirrer. After a fixed time, the liquid product was neutralized with sulfuric acid and filtered to remove Ba²⁺. The filtrate was added equal mole of NaOH to prevent organic acids lose during freeze-dry. After freeze-drying, the products were acidified with HCl and used as the substrates in the amination step. The liquid products were analyzed by HPLC (Shimadzu LC-20A) equipped with both RI and UV detectors. Glucose and hydroxyl acids were quantified on an Agilent Hi-Plex H column (7.7 × 300 mm, 8 μm) using a dilute H₂SO₄ aqueous solution as the mobile phase, whereas amino acids were analyzed on a Poroshell 120 EC-C8 column (4.6 × 100 mm) by using a precolumn derivatization method, where ortho-phthalaldehyde was used as the derivatization reagent. The dehydrogenation of isopropanol (IPA) over Ru and Pd catalysts

was performed in a fixed bed flow reactor equipped with an online gas chromatography (GC, Agilent 7890A). A flame ionization detector (FID) and an Agilent Cyclodex-B column (30 m × 250 μm × 0.25 μm) were used to detect and analyze IPA and gas products.

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